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I, LEANNE MYNOTT, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PQ 0663 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. filed on 31 May 1999.

## PRIORITY DOCUMENT

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Twenty-sixth day of May 2000

LEANNE MYNOTT  
TEAM LEADER EXAMINATION  
SUPPORT AND SALES



Fujisawa Pharmaceutical Co., Ltd.

**A U S T R A L I A**  
**Patents Act 1990**

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**PROVISIONAL SPECIFICATION**  
for the invention entitled:

"Antifungal combination use"

The invention is described in the following statement:

DESCRIPTION

## ANTIFUNGAL COMBINATION USE

5 TECHNICAL FIELD

The present invention relates to antifungal combination use of known antifungal agents such as the azoles or polyenes in combination with a lipopeptide compound antifungal agent. More particularly, the invention relates to antifungal combination use of azoles such as fluconazole (hereinafter referred to as FLCZ), voriconazole, itraconazole (hereinafter referred to as ITCZ), ketoconazole, miconazole, ER 30346, SCH 56592; polyenes such as amphotericin B (hereinafter referred to as AMPH-B), nystatin or liposomal and lipid forms thereof such as Abelcet, AmBisome and Amphocil; purine or pyrimidine nucleotide inhibitors such as flucytosine; or polyoxins such as nikkomycins, in particular nikkomycin Z or other chitin inhibitors, elongation factor inhibitors such as sordarin and analogs thereof, mannan inhibitors such as predamycin, bactericidal/permeability-inducing (BPI) protein products such as XMP.97 or XMP.127 or complex carbohydrate antifungal agents such as CAN-296 in combination with a lipopeptide compound [I] of the following formula:

Wherein R<sup>1</sup> is acyl group,  
R<sup>2</sup> is hydrogen or hydroxy and  
R<sup>3</sup> is hydrogen or hydroxy,  
or a salt thereof.

These combination uses have been shown to be useful against such opportunistic pathogens as *Cryptococcus*, *Candida*, *Aspergillus*, *Histoplasma*, *Coccidioides*, *Paracoccidioides*, *Blastomyces*, *Fusarium*, *Sporothrix*, *Trichosporon*, *Rhizopus*, *Pseudallescheria*, dermatophytes, *Paecilomyces*, *Alternaria*, *Curvularia*, *Exophiala*, *Wangiella*, *Penicillium*, *Saccharomyces*, Dematiaceous fungi and *Pneumocystis carinii*.

There is an increasing need for agents which are effective against opportunistic mycotic infections by such agents as *Cryptococcus*, *Candida*, *Aspergillus*, *Histoplasma*, *Coccidioides*, *Paracoccidioides*, *Blastomyces*, *Fusarium*, *Sporothrix*, *Trichosporon*, *Rhizopus*, *Pseudallescheria*,

dermatophytes, *Paecilomyces*, *Alternaria*, *Curvularia*,  
*Exophiala*, *Wangiella*, *Penicillium*, *Saccharomyces*,  
*Dematiaceae* fungi and *Pneumocystis carinii*. The present  
uses, i.e., polyenes, such as amphotericin B, cause severe  
side effects and azoles, such as fluconazole, are only  
fungistatic. The lipopeptide compound [I] is cyclic  
hexapeptide which inhibits cell wall 1,3 $\beta$ -D-glucan synthesis.  
The lipopeptide compound [I] has shown potent *in vivo*  
activity against *Candida*, *Pneumocystis carinii*, *Aspergillus*,  
as well as the other fungal pathogens listed above.

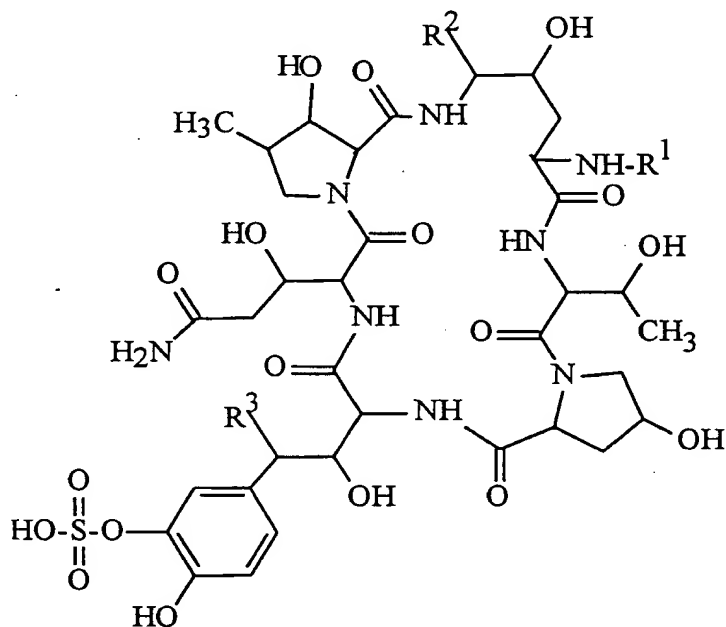
Combination use with antifungal drugs may provide  
additional options for treating *Aspergillus* and other  
fungal pathogens.

Previous studies have evaluated the efficacy of other  
lipopeptide compounds against *Cryptococcus neoformans* in  
combination with amphotericin B and fluconazole (Abruzzo et  
al., Antimicrob. Agents Chemo. 1995, 39:1077-1081 and  
Bartizal et al., Antimicrob. Agents Chemo. 1995, 39:1070-  
1076). However, none of these studies have demonstrated  
the results found using the lipopeptide compound [I].

#### DISCLOSURE OF THE INVENTION

The present invention relates to antifungal  
combination use of known antifungal agents such as the  
azoles or polyenes in combination with a lipopeptide  
compound antifungal agent. More particularly, the present  
invention relates to antifungal combination use of azoles  
such as fluconazole, voriconazole, itraconazole,  
ketoconazole, miconazole, ER 30346, SCH 56592; polyenes  
such as amphotericin B, nystatin or liposomal and lipid  
forms thereof such as Abelcet, AmBisome and Amphocil;  
purine or pyrimidine nucleotide inhibitors such as  
flucytosine; or polyoxins such as nikkomycins, in  
particular nikkomycin Z or other chitin inhibitors,  
elongation factor inhibitors such as sordarin and analogs

thereof, mannan inhibitors such as predamycin,  
 bactericidal/permeability-inducing (BPI) protein products  
 such as XMP.97 or XMP.127 or complex carbohydrate  
 antifungal agents such as CAN-296 in combination with a  
 5 lipopeptide compound [I] of the following formula:



[I]

Wherein R<sup>1</sup> is acyl group,  
 R<sup>2</sup> is hydrogen or hydroxy and  
 10 R<sup>3</sup> is hydrogen or hydroxy,  
 or a salt thereof.

Suitable salt of the lipopeptide compound [I] is a  
 pharmaceutically acceptable and conventional non-toxic salt,  
 15 and may include a salt with a base or an acid addition salt  
 such as a salt with an inorganic base, for example, an  
 alkali metal salt (e.g., sodium salt, potassium salt, etc.),  
 an alkaline earth metal salt (e.g., calcium salt, magnesium  
 salt, etc.), an ammonium salt;  
 20 a salt with an organic base, for example, an organic amine  
 salt (e.g., triethylamine salt, diisopropylethylamine salt,

pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.);

5 an inorganic acid addition salt (e.g., hydrochloride hydrobromide, sulfate, phosphate, etc.);

an organic carboxylic sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.);

10 a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

It is to be noted that each of the lipopeptide compound [I] may include one or more stereoisomer(s) such  
15 as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s), and all such isomer(s) and the mixture thereof are included within the scope of the present invention.

The lipopeptide compound [I] or a salt thereof  
20 includes solvated compound [e.g., enclosure compound (e.g., hydrate, etc.)].

The lipopeptide compound [I] or a salt thereof includes both its crystal form and non-crystal form.

It should be understood that the lipopeptide compound  
25 [I] in the present invention may include the prodrug form.

Suitable example of "acyl group" may include aliphatic acyl, aromatic acyl, arylaliphatic acyl and heterocyclic-aliphatic acyl derived from carboxylic acid, carbonic acid,  
30 carbamic acid, sulfonic acid, and the like.

Suitable example of said "acyl group" may be illustrated as follows.

Aliphatic acyl such as lower or higher alkanoyl (e.g.,  
35 formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl,

pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.);

lower or higher alkoxy-carbonyl (e.g., methoxy-carbonyl, ethoxy-carbonyl, t-butoxy-carbonyl, t-pentyloxy-carbonyl, heptyloxy-carbonyl, etc.);

lower or higher alkylsulfonoyl (e.g., methylsulfonoyl, ethylsulfonoyl, etc.);

lower or higher alkoxy-sulfonoyl (e.g., methoxy-sulfonoyl, ethoxy-sulfonoyl, etc.); or the like;

Aromatic acyl such as

aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.); aroyl

which has one or more suitable substituent(s);

ar(lower)alkanoyl [e.g., phenyl(C<sub>1</sub>-C<sub>6</sub>)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(C<sub>1</sub>-C<sub>6</sub>)alkanoyl (e.g., naphthylacetyl,

naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];

ar(lower)alkenoyl [e.g., phenyl(C<sub>3</sub>-C<sub>6</sub>)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentanoyl, phenylhexenoyl, etc.), naphthyl(C<sub>3</sub>-C<sub>6</sub>)alkenoyl (e.g., naphthylpropenoyl,

naphthylbutenoyl, etc.), etc.];

ar(lower)alkoxy-carbonyl [e.g., phenyl(C<sub>1</sub>-C<sub>6</sub>)alkoxy-carbonyl (e.g., benzyloxy-carbonyl, etc.), fluorenyl(C<sub>1</sub>-C<sub>6</sub>)alkoxy-carbonyl (e.g., fluorenylmethyloxy-carbonyl, etc.), etc.];

aryloxy-carbonyl (e.g., phenoxy-carbonyl,

naphthyloxy-carbonyl, etc.);

aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.);

arylcarbamoyle (e.g., phenylcarbamoyle, etc.);

arylthiocarbamoyle (e.g., phenylthiocarbamoyle, etc.);



arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl, etc.);

arylsulfonyl which may have 1 to 4 lower alkyl (e.g., phenylsulfonyl, p-tolylsulfonyl, etc.); or the like;

5 Heterocyclic acyl such as

heterocycliccarbonyl; heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclicpropanoyl, heterocyclicbutanoyl, heterocyclicpentanoyl, heterocyclichexanoyl, etc.);

10 heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, heterocyclichexenoyl, etc.);

heterocyclicglyoxyloyl; or the like.

15 Among them, more preferred "acyl group" is aroyl which has one or more suitable substituent(s).

Suitable example of "suitable substituent(s)" in the term of "aroyl which has one or more suitable substituent(s)" may be heterocyclic group substituted with  
 20 aryl having lower alkoxy, heterocyclic group substituted with aryl having lower alkoxy(lower)alkoxy, heterocyclic group substituted with aryl having lower alkoxy(higher)alkoxy, heterocyclic group substituted with aryl having cyclo(lower)alkyloxy, heterocyclic group  
 25 substituted with aryl having heterocyclic group, heterocyclic group substituted with cyclo(lower)alkyl having cyclo(lower)alkyl, heterocyclic group substituted with aryl having aryl substituted with lower alkoxy(lower)alkoxy, heterocyclic group substituted with  
 30 aryl having heterocyclic group substituted with cyclo(lower)alkyl;

in which the preferred one may be unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl  
 35 having (C<sub>4</sub>-C<sub>6</sub>)alkoxy, unsaturated condensed heterocyclic

- group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C<sub>4</sub>-C<sub>6</sub>)alkoxy, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C<sub>1</sub>-C<sub>4</sub>)alkoxy-
- 5 (C<sub>4</sub>-C<sub>6</sub>)alkoxy, unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>7</sub>-C<sub>14</sub>)alkoxy, saturated 3 to 8-membered heteromonocyclic
- 10 group containing 1 to 4 nitrogen atom(s) substituted with phenyl having (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>7</sub>-C<sub>14</sub>)alkoxy, unsaturated condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having cyclo(C<sub>4</sub>-C<sub>6</sub>)alkoxy, unsaturated condensed
- 15 heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl saturated 3 to 8-membered heteromonocyclic group containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), saturated 3 to 8-membered heteromonocyclic group containing 1 to 4
- 20 nitrogen atom(s) substituted with cyclo(C<sub>4</sub>-C<sub>6</sub>)alkyl having cyclo(C<sub>4</sub>-C<sub>6</sub>)alkyl, unsaturated 3 to 8-membered
- 
- heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having phenyl substituted with (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>)alkoxy,
- 25 unsaturated 3 to 8-membered heteromonocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) substituted with cyclo(C<sub>4</sub>-C<sub>6</sub>)alkyl, unsaturated
- 30 condensed heterocyclic group containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s) substituted with phenyl having saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) having cyclo(C<sub>4</sub>-C<sub>6</sub>)alkyl, etc.

Among them, the most preferred one may be isoxazolyl substituted with phenyl having pentyloxy, imidazothiadiazolyl substituted with phenyl having pentyloxy, thiadiazolyl substituted with phenyl having methoxyhexyloxy, thiadiazolyl substituted with phenyl having methoxyoctyloxy, thiadiazolyl substituted with phenyl having methoxyheptyloxy, imidazothiadiazolyl substituted with phenyl having cyclohexyloxy, imidazothiadiazolyl substituted with phenyl having dimethylmorpholino, piperazinyl substituted with phenyl having methoxyheptyloxy, piperazinyl substituted with phenyl having methoxyoctyloxy, piperazinyl substituted with cyclohexyl having cyclohexyl, thiadiazolyl substituted with phenyl having phenyl substituted with methoxyethoxy, thiadiazolyl substituted with phenyl having phenyl substituted with methoxybutoxy, thiadiazolyl substituted with phenyl having phenyl substituted with ethoxypropoxy, imidazothiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl, imidazothiadiazolyl substituted with phenyl having piperazinyl substituted with cyclohexyl.

The more suitable example of "acyl group" of  $R^1$  may be benzoyl which has isoxazolyl substituted with phenyl having pentyloxy, benzoyl which has imidazolthiadiazolyl substituted with phenyl having pentyloxy, benzoyl which has thiadiazolyl substituted with phenyl having methoxyhexyloxy, benzoyl which has thiadiazolyl substituted with phenyl having methoxyoctyloxy, benzoyl which has thiadiazolyl substituted with phenyl having methoxyheptyloxy, benzoyl which has imidazothiadiazolyl substituted with phenyl having cyclohexyloxy, benzoyl which has imidazothiadiazolyl substituted with phenyl having dimethylmorpholino, benzoyl which has piperazinyl substituted with phenyl having methoxyheptyloxy, benzoyl which has piperazinyl substituted

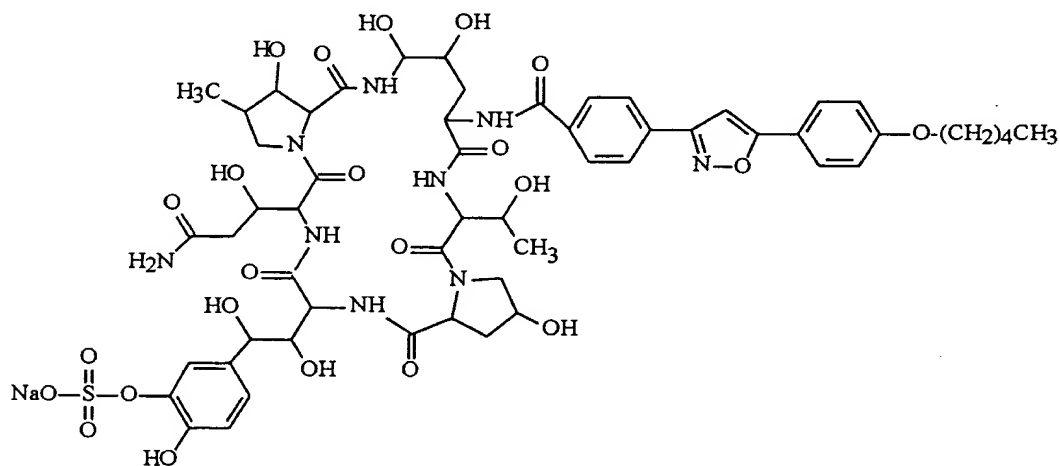
with phenyl having methoxyoctyloxy, benzoyl which has  
 piperazinyl substituted with cyclohexyl having cyclohexyl,  
 benzoyl which has thiadiazolyl substituted with phenyl  
 having phenyl substituted with methoxyethoxy, benzoyl which  
 5 has thiadiazolyl substituted with phenyl having phenyl  
 substituted with methoxybutoxy, benzoyl which has  
 thiadiazolyl substituted with phenyl having phenyl  
 substituted with ethoxypropoxy, benzoyl which has  
 imidazothiadiazolyl substituted with phenyl having  
 10 piperazinyl substituted with cyclohexyl, benzoyl which has  
 imidazothiadiazolyl substituted with phenyl having  
 piperazinyl substituted with cyclohexyl.

In particular, this combination use has been shown  
 15 to be useful against such opportunistic pathogens as  
*Cryptococcus*, *Candida*, *Aspergillus*, *Histoplasma*,  
*Coccidioides*, *Paracoccidioides*, *Blastomyces*, *Fusarium*,  
*Sporothrix*, *Trichosporon*, *Rhizopus*, *Pseudallescheria*,  
 dermatophytes, *Paecilomyces*, *Alternaria*, *Curvularia*,  
 20 *Exophiala*, *Wangiella*, *Penicillium*, *Saccharomyces*,  
~~Dematiaceous fungi and *Pneumocystis carinii*.~~

The lipopeptide compound [I], its preparation, its  
 dosage, etc. are disclosed in U.S. Patent Nos. 5,376,634,  
 5,569,946 and WO96/11210, the disclosures of which are  
 25 incorporated herein by reference.

The azole, polyene or other antifungal agent may be  
 administered orally or parenterally. The lipopeptide  
 compound [I] is preferably administered parenterally, but  
 is not limited to that route and may also be administered  
 30 by other routes such as oral, intramuscular or subcutaneous.

The invention is further described in connection with  
 the following non-limiting examples.

EXAMPLESTest Compound

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Test Method

The broth microdilution method using RPMI medium (pH7.0) was used, comparing the each drug alone (Test Compound, AMPH-B and ITCZ) and combined for each clinical isolates of *Aspergillus fumigatus*. A combination of drug concentrations was evaluated by the checkerboarded method.

All tubes were examined macroscopically for growth and compared to a control (no drug). MIC was visually determined as the lowest concentration resulting in prominent decrease in turbidity compared to controls.

The Fractional Inhibitory Concentration (FIC) for each drug in mixture wells was compared to the MIC for each drug alone. The FIC index was calculated from the sum of the FICs for the two drugs. A quantitative expression of the interaction for inhibition is as follows:

Synergy  $\leq 0.5$ ;

Test Result

In vitro combination with Test Compound and AMPH-B against

5 *A. fumigatus*

Organism	MIC ( $\mu\text{g/mL}$ )				FIC index
	Test Compound Alone	Test Compound Combination	AMPH-B alone	AMPH-B combination	
<i>A. fumigatus</i> 8004	0.0313	0.0078	2	0.5	0.50

In vitro combination with Test Compound and ITCZ against *A. fumigatus*

Organism	MIC ( $\mu\text{g/mL}$ )				FIC index
	Test Compound Alone	Test Compound combination	ITCZ alone	ITCZ combination	
<i>A. fumigatus</i> 8008	0.0313	0.0078	0.5	0.125	0.50

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From the results of the above example, synergy effect of efficacy was observed with combination of the lipopeptide compound [I] and amphotericin B or itraconazole at certain concentrations. No antagonism of efficacy with amphotericin B or itraconazole in combination with the lipopeptide compound [I] also was seen.

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We also have examined in vitro combination with the lipopeptide compound [I] and amphotericin B or itraconazole against *C. albicans* and *C. neoformans*. From the result, synergy effect of efficacy was observed with combination of the lipopeptide compound [I] and amphotericin B or itraconazole at certain concentrations.

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Given the above disclosure, it is thought that variations will occur to those skilled in the art. For

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example, it is thought that combination using azoles other than amphotericin B or itraconazole and the lipopeptide compounds other than the lipopeptide compound [I] may also be effective against fungal infections caused by the fungal pathogens noted. Accordingly, it is intended that the above examples should be construed as illustrative and that the invention disclosed herein should be limited only by the following claims.

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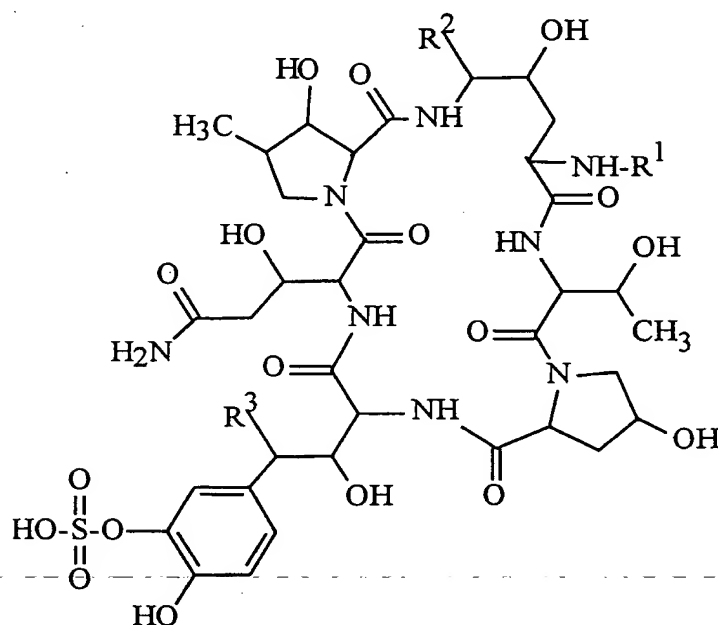
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CLAIMS

1. A method for treatment or inhibition of the infectious diseases caused by the fungal pathogen which comprises administering an effective amount of a lipopeptide compound [I] of the following formula:



[I]

Wherein  $R^1$  is acyl group,  
 $R^2$  is hydrogen or hydroxy and  
 $R^3$  is hydrogen or hydroxy,  
 or a salt thereof, in combination with an azole,  
 polyene, purine nucleotide inhibitor, pyrimidine  
 nucleotide inhibitor, mannan inhibitor, protein  
 elongation factor inhibitor, bactericidal/permeability  
 inducing protein product or polyoxin.

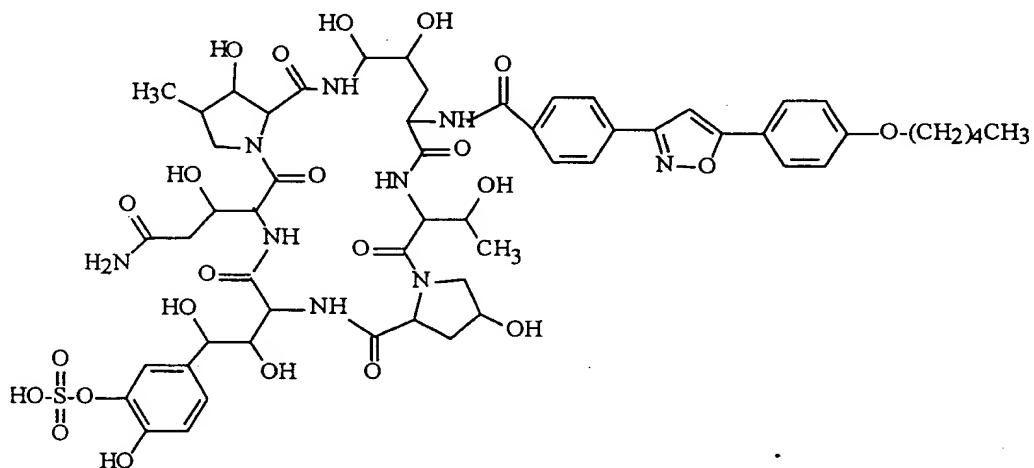
2. The method of Claim 1 which comprises administering an effective amount of a lipopeptide compound [I] in combination with a polyene.



3. The method of Claim 1 which comprises administering an effective amount of a lipopeptide compound [I] in combination with an azole.

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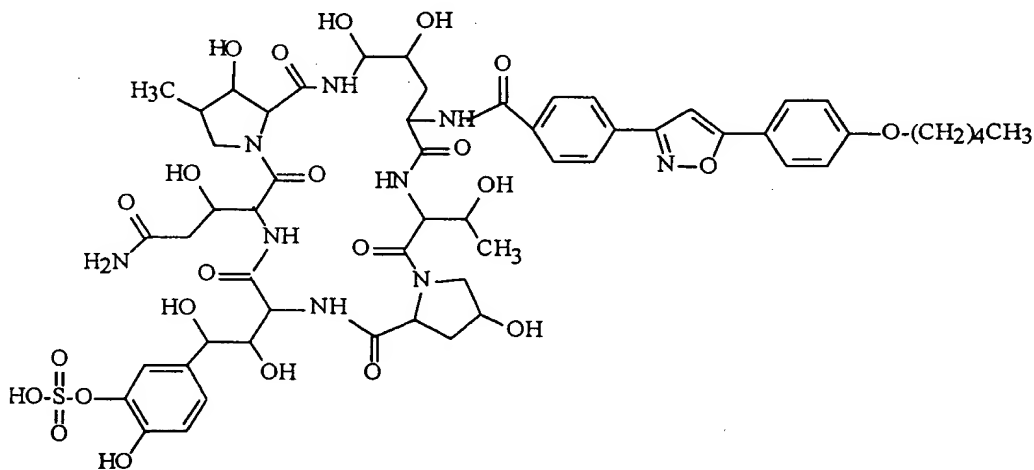
4. The method of Claim 1 wherein the lipopeptide compound [I] is



or a thereof.

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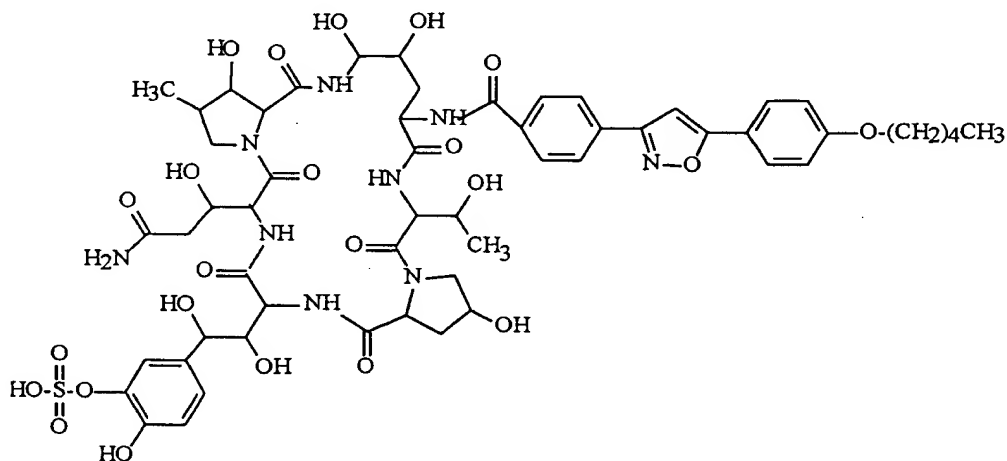
5. The method of Claim 2 wherein the lipopeptide compound [I] is



or a salt thereof.

6. The method of Claim 3 wherein the lipopeptide compound [I] is

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or a salt thereof.

7. The method of Claim 1 wherein the azole is selected from the group consisting of fluconazole, voriconazole, itraconazole, ketoconazole, miconazole, ER 30346, SCH 56592; the polyenes is selected from the group consisting of amphotericin B, nystatin or liposomal and lipid forms thereof; the purine or pyrimidine nucleotide inhibitors is flucytosine; the polyoxin is nikkomycin Z, the elongation factor inhibitor is sordarin and analogs thereof and the mannan inhibitor is predamycin.

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8. The method of Claim 7 wherein the polyene is Amphotericin B.
9. The method of Claim 7 wherein the azole is Fluconazole.

10. The method of Claim 7 wherein the polyene is Itraconazole.

- 5 11. The method of Claim 1 wherein the infectious diseases are caused by a fungal pathogen selected from *Cryptococcus*, *Candida*, *Aspergillus*, *Histoplasma*, *Coccidioides*, *Paracoccidioides*, *Blastomyces*, *Fusarium*, *Sporothrix*, *Trichosporon*, *Rhizopus*, *Pseudallescheria*,  
10 dermatophytes, *Paecilomyces*, *Alternaria*, *Curvularia*, *Exophiala*, *Wangiella*, *Penicillium*, *Saccharomyces*, *Dematiaceous* fungi or *Pneumocystis carinii*.
12. The method of Claim 2 wherein the infectious diseases  
15 are caused by the fungal pathogen selected from *Cryptococcus*, *Candida*, *Aspergillus*, *Histoplasma*, *Coccidioides*, *Paracoccidioides*, *Blastomyces*, *Fusarium*, *Sporothrix*, *Trichosporon*, *Rhizopus*, *Pseudallescheria*, dermatophytes, *Paecilomyces*, *Alternaria*, *Curvularia*,  
20 *Exophiala*, *Wangiella*, *Penicillium*, *Saccharomyces*, *Dematiaceous* fungi or *Pneumocystis carinii*.
13. The method of Claim 3 wherein the infectious diseases  
25 are caused by the fungal pathogen selected from *Cryptococcus*, *Candida*, *Aspergillus*, *Histoplasma*, *Coccidioides*, *Paracoccidioides*, *Blastomyces*, *Fusarium*, *Sporothrix*, *Trichosporon*, *Rhizopus*, *Pseudallescheria*, dermatophytes, *Paecilomyces*, *Alternaria*, *Curvularia*, *Exophiala*, *Wangiella*, *Penicillium*, *Saccharomyces*,  
30 *Dematiaceous* fungi or *Pneumocystis carinii*.
14. The method of Claim 11 wherein the fungal pathogen is selected from *Cryptococcus*, *Candida* or *Aspergillus*.
- 35 15. The method of Claim 12 wherein the fungal pathogen is

selected from *Cryptococcus*, *Candida* or *Aspergillus*.

16. The method of Claim 13 wherein the fungal pathogen is selected from *Cryptococcus*, *Candida* or *Aspergillus*.

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17. A pharmaceutical composition for the prophylactic and/or therapeutic treatment of the infectious diseases caused by the fungal pathogen which comprises the lipopeptide compound [I] in claim 1 in combination with an azole, polyene, purine nucleotide inhibitor, pyrimidine nucleotide inhibitor, mannan inhibitor, protein elongation factor inhibitor, bactericidal/permeability inducing protein product or polyoxin and optionally pharmaceutically carriers or excipients.

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18. Use of the lipopeptide compound [I] in claim 1 in combination with an azole, polyene, purine nucleotide inhibitor, pyrimidine nucleotide inhibitor, mannan inhibitor, protein elongation factor inhibitor, bactericidal/permeability inducing protein-product or polyoxin for the manufacture of medicament for simultaneous, separate or sequential use for the prevention and/or treatment of the infectious diseases caused by the fungal pathogen.

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ABSTRACT

There is described antifungal combination use of known  
5 antifungal agents such as the azoles or polyenes in  
combination with a lipopeptide compound antifungal agent.  
More particularly, the invention relates to antifungal  
combination use of azoles such as fluconazole, voriconazole,  
itraconazole, ketoconazole, miconazole, ER 30346, SCH  
10 56592; polyenes such as amphotericin B, nystatin or  
liposomal and lipid forms thereof such as Abelcet, AmBisome  
and Amphocil; purine or pyrimidine nucleotide inhibitors  
such as flucytosine; or polyoxins such as nikkomycins, in  
particular nikkomycin Z or other chitin inhibitors,  
15 elongation factor inhibitors such as sordarin and analogs  
thereof, mannan inhibitors such as predamycin,  
bactericidal/permeability-inducing (BPI) protein products  
such as XMP.97 or XMP.127 or complex carbohydrate  
antifungal agents such as CAN-296 in combination with a  
20 lipopeptide compound [I] as described herein.

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